1268835

PATENT SPECIFICATION

(11) 1268835

NO DRAWINGS

(21) Application No. 30406/69 (22) Filed 16 June 1969

(31) Convention Application No. P 17 70 731.2

(32) Filed 27 June 1968 in

(33) Germany (DT)

(45) Complete Specification published 29 March 1972

(51) International Classification C 07 d 57/00 99/02 A 61 k 27/00

(52) Index at acceptance

C2C 171—27X—289 17X—271—289 181—27X—282 187—196—197 215 220 22Y 250 252 255 256 25Y 28X 305 30Y 313 31Y 321 32Y 337 342 34Y 364 36Y 373 37Y 385 510 511 51X 535 539 620 650 652 672 790 79Y SD

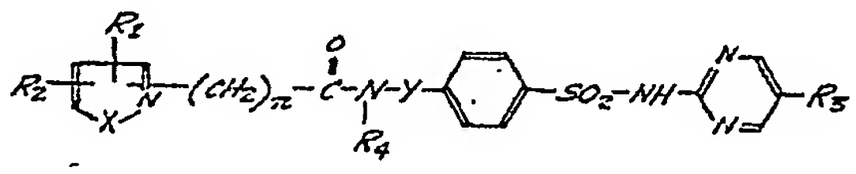
A5B 332 33Y 38Y 393 411 41X 41Y

(54) NEW SULPHONAMIDES HAVING A BLOOD SUGAR LOWERING ACTION

(71) We, SCHERING AKTIENGESELLSCHAFT, a Body Corporate organised according to the laws of Germany, of Berlin and Bergkamen, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with new sulphonamides having a blood sugar lowering action and with their manufacture and use.

The present invention provides sulphonamides of the general formula



in which R_1 and R_2 are identical or different and each represents a hydrogen or halogen atom or an alkyl, alkoxy or alkylmercapto group containing 1 to 4 carbon atoms, R_3 represents an alkyl or cycloalkyl group containing up to 8 carbon atoms which may be interrupted by at least one oxygen atom, or represents an alkoxy or cycloalkoxy group containing up to 8 carbon atoms in which the alkyl or cycloalkyl part, respectively, may be interrupted by at least one oxygen atom, R_4 represents a hydrogen atom or an alkyl group containing 1 to 4 carbon atoms, X represents an oxygen or sulphur atom or an NH group, Y represents an alkylene group containing 1 to 4 carbon atoms and *n* represents 0 or an integer from 1 to 4, as well as their salts with physiologically tolerable bases.

The new compounds possess a very good activity as antidiabetics. Thus the new compounds show a lowering of the blood sugar level by up to more than 35% of the initial value in the case of rats, at doses of 0.1—1.0 mg/kg of body weight and using the standard methods of measurement.

For therapeutic use, the new compounds can be administered as the free sulphonamides or as salts with physiologically tolerable bases. As bases there may be mentioned, for example, sodium, lithium, calcium and ammonium hydroxide and amines, for example methylglucamine, morpholine and ethanolamine. It is possible to administer mixtures of the free sulphonamides with a suitable alkali metal carbonate or alkali metal bicarbonate. Salts of the sulphonamides with bases which themselves also possess a blood sugar-lowering action, for example butyl biguanide, are of particular value.

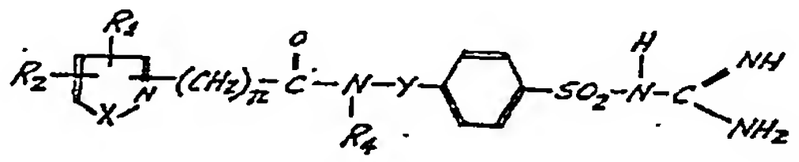
The new sulphonamides and their salts with physiologically tolerable bases can be made up with or without, for example, the additives, excipients and flavour correctants which are normally used in galenical pharmacy. Accordingly, the present invention also provides pharmaceutical preparations which comprise these compounds in admixture or conjunction with a pharmaceutically suitable carrier. The

[*Price 25p*]

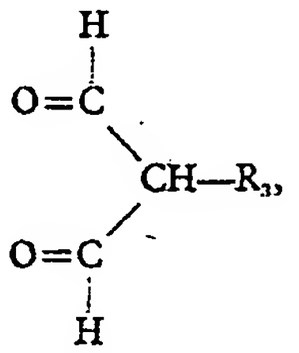
pharmaceutical preparations may in particular, for example, be in a powder form, for example as tablets, dragées, capsules or pills, or in the form of suspensions or solutions.

The new sulphonamides may be manufactured by

a) subjecting a compound of the general formula

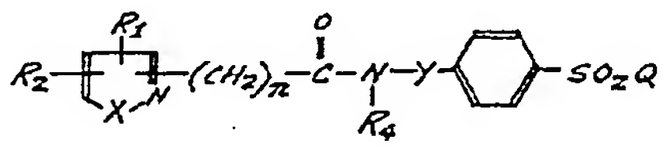


in which R_1, R_2, R_3, n, X and Y have the meanings given above, to a ring-closing condensation with a substituted malondialdehyde of the general formula



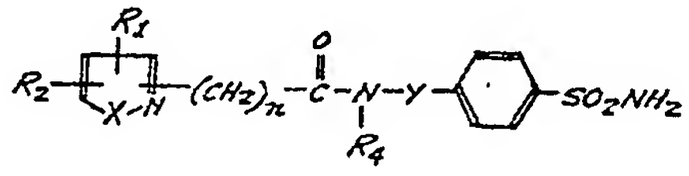
in which R_3 has the meaning given above and in which the aldehyde groups may be functionally modified, or

b) reacting a compound of the general formula

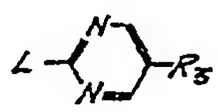


in which R_1, R_2, R_3, n, X and Y have the meanings given above and Q represents a halogen atom, preferably a chlorine atom, with a 2-amino-5-R_3-pyrimidine, in which R_3 has the meaning given above, or

c) reacting a compound of the general formula

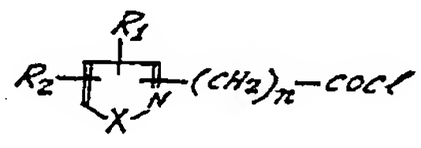


in which R_1, R_2, R_3, n, X and Y have the meanings given above, in the free form or as an alkali metal salt, with a compound of the general formula

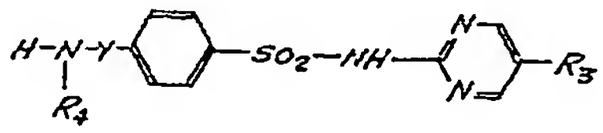


in which R_3 has the meaning given above and L represents a halogen atom, preferably a chlorine atom, a trialkylammonium group or an alkylsulphonyl group containing 1 to 4 carbon atoms, or

d) allowing a compound of the general formula

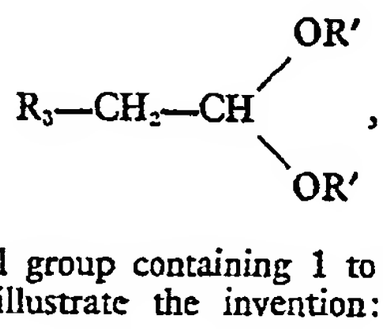


in which R_1, R_2, n and X have the meanings given above, or another derivative of the corresponding acid having equivalent reactivity, to react with an amine of the general formula



in which R_3, R_4 and Y have the meanings given above, and, if desired, converting the resulting compound into a salt thereof with a physioligically tolerable base.

The malondialdehyde derivatives used for the reaction according to method (a) can be obtained, for example, by formylating by a known method an aldehyde-acetal of the general formula



in which R′ represents an alkyl group containing 1 to 8 carbon atoms.

The following Examples illustrate the invention:

Example 1

33 g of 2 - (4 - β - aminoethylbenzenesulphonamido) - 5 - isobutylpyrimidine (manufactured by the reaction of carbethoxyaminoethylbenzene-sulphochloride with 2-amino-5-isobutylpyrimidine and subsequent saponification of the carbethoxyaminoethyl group to give the aminoethyl group, melting point 223°C) were dissolved in 100 ml of pyridine and after the addition of 16 g of 5-methylisoxazole-3-carboxylic acid chloride were heated for 2 hours at 60°C. The pyridine was then distilled off and the residue was mixed with water. After acidifying with hydrochloric acid the resulting precipitate was filtered off with suction and recrystallized from methylglycol. 30 g of 2 - {4 - [β - (5 - methylisoxazole - 3 - carbonamido) - ethyl] - benzenesulphonamido} - 5 - isobutylpyrimidine of melting point 223°C were thus obtained.

The following sulphonamides were obtained in an analogous manner by using corresponding starting materials:

2 - {4 - [β - (5 - Methylisoxazole - 3 - carbonamido) - ethyl] - benzenesulphonmido} - 5 - *n* - butoxypyrimidine, melting point 195°C,

2 - {4 - [β - (5 - Methylisoxazole - 3 - carbonamido) - ethyl] - benzenesulphonamido} - 5 - isopropoxypyrimidine, melting point 221°C,

2 - {4 - [β - (5 - Methylisoxazole - 3 - carbonamido) - ethyl] - benzenesulphonamido} - 5 - methoxyethoxypyrimidine, melting point 205°C,

2 - [4 - (5 - Methylisoxazole - 3 - carbonamido) - methylbenzenesulphonamido] - 5 - isobutylpyrimidine, melting point 253°C,

2 - {4 - [β - (3,5 - Bis - methylmercaptoisothiazole - 4 - carbonamido) - ethyl] - benzenesulphonamido} - 5 - *n* - propoxypyrimidine, melting point 182°C,

2 - {4 - [β - (3,4 - Dichloroisothiazole - 5 - carbonamido) - ethyl] - benzenesulphonamido} - 5 - isopropoxypyrimidine, melting point 202—203°C, and

2 - {4 - [β - (4 - Chloro - 5 - methylisoxazole - 3 - carbonamido) - ethyl] - benzenesulphonamido} - 5 - isopropoxypyrimidine, melting point 138°C.

Example 2

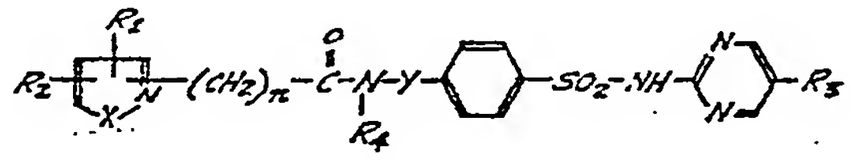
35 g of 4 - [β - (3 - methylpyrazole - 5 - carbonylamino) - ethyl] - benzenesulphoguanidine (melting point 268°C) were heated for 5 hours at the boil with a solution of 16 g of α-isobutyl-β-dimethylaminoacrolein (manufactured according to the method of Vilsmeier from isobutylacetaldehyde-diethylacetal), boiling point (0.03 mm Hg) 106°C, and 3 g of sodium in 250 ml of methanol. The methanol was then distilled off and the residue was dissolved in water. After clarifying the solution with charcoal a precipitate was obtained by acidification with hydrochloric acid which, when recrystallized from methylglycol, yielded 29 g of 2 - {4 - [β - (3 - methylpyrazole - 5 - carbonamido) - ethyl] - benzenesulphonamido} - 5 - isobutylpyrimidine of melting point 243°C.

EXAMPLE 3

33 g of sodium 4 - [β - (5 - methylisoxazole - 3 - carbonamido) - ethyl] - benzenesulphonamide (melting point 216°C) were dissolved in 250 ml of acetamide and stirred for 6 hours at 150°C with 16.5 g of 2-chloro-5-isopropoxypyrimidine. The acetamide was then distilled off and the residue was mixed with water. A precipitate was obtained which after recrystallization from methylglycol yielded 28 g of 2 - {4 - [β - (5 - methylisoxazole - 3 - carbonamido) - ethyl] - benzenesulphonamido} - 5 - isopropoxypyrimidine of melting point 218°C.

WHAT WE CLAIM IS:—

1. A sulphonamide of the general formula



in which R_1 and R_2 each represents a hydrogen or halogen atom or an alkyl, alkoxy or alkylmercapto group containing 1 to 4 carbon atoms, R_3 represents an alkyl or cycloalkyl group containing up to 8 carbon atoms which may be interrupted by at least one oxygen atom, or represents an alkoxy or cycloalkoxy group containing up to 8 carbon atoms in which the alkyl or cycloalkyl part, respectively, may be interrupted by at least one oxygen atom, R_4 represents a hydrogen atom or an alkyl group containing 1 to 4 carbon atoms, X represents an oxygen or sulphur atom or an NH group, Y represents an alkylene group containing 1 to 4 carbon atoms and *n* represents 0 or an integer from 1 to 4.

2. A salt of a sulphonamide as claimed in claim 1 with a physiologically tolerable base.

3. 2 - {4 - [β - (5 - Methylisoxazole - 3 - carbonamido) - ethyl] - benzenesulphonamido} - 5 - isobutylpyrimidine.

4. 2 - {4 - [β - (5 - Methylisoxazole - 3 - carbonamido) - ethyl] - benzenesulphonamido} - 5 - *n* - butoxypyrimidine.

5. 2 - {4 - [β - (5 - Methylisoxazole - 3 - carbonamido) - ethyl] - benzenesulphonamido} - 5 - isopropoxypyrimidine.

6. 2 - {4 - [β - (5 - Methylisoxazole - 3 - carbonamido) - ethyl] - benzenesulphonamido} - 5 - methoxyethoxypyrimidine.

7. 2 - [4 - (5 - Methylisoxazole - 3 - carbonamido) - methylbenzenesulphonamido] - 5 - isobutylpyrimidine.

8. 2 - {4 - [β - (3,5 - Bis - methylmercaptoisothiazole - 4 - carbonamido) - ethyl] - benzenesulphonamido} - 5 - *n* - propoxypyrimidine.

9. 2 - {4 - [β - (3 - Methylpyrazole - 5 - carbonamido) - ethyl] - benzenesulphonamido} - 5 - isobutylpyrimidine.

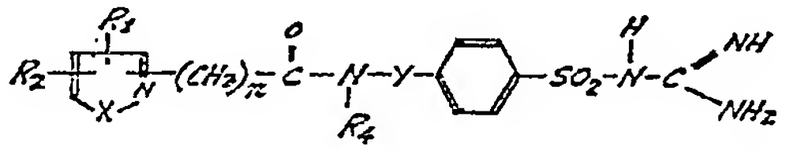
10. 2 - {4 - [β - (3,4 - Dichloroisothiazole - 5 - carbonamido) - ethyl] - benzenesulphonamido} - 5 - isopropoxypyrimidine.

11. 2 - {4 - [β - (4 - Chloro - 5 - methylisoxazole - 3 - carbonamido) - ethyl] - benzenesulphonamido} - 5 - isopropoxypyrimidine.

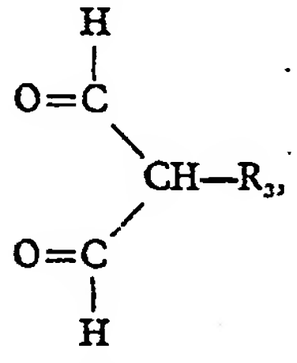
12. A salt of the sulphonamide claimed in any one of claims 3 to 11 with a physiologically tolerable base.

13. A process for the manufacture of a compound as claimed in claim 1 or a salt thereof with a physiologically tolerable base, wherein

a) a compound of the general formula

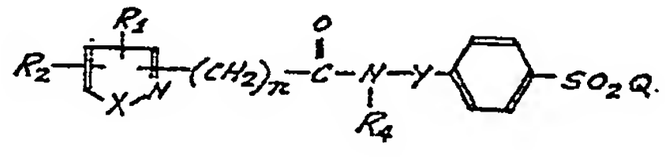


in which R_1, R_2, R_4, *n*, X and Y have the meanings given in claim 1, is subjected to a ring-closing condensation with a substituted malondialdehyde of the general formula



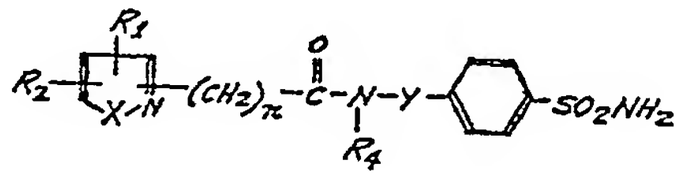
in which R_3 has the meaning given in claim 1 and in which the aldehyde groups may be functionally modified, or

b)

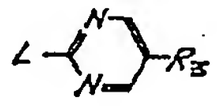


in which R_1, R_2, R_3, n, X and Y have the meanings given in claim 1 and Q represents a halogen atom, is reacted with a 2-amino-5-R_3-pyrimidine, in which R_3 has the meaning given in claim 1, or

c) a compound of the general formula

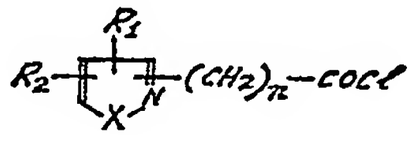


in which R_1, R_2, R_4, n, X and Y have the meanings given in claim 1, or an alkali metal salt thereof, is reacted with a compound of the general formula

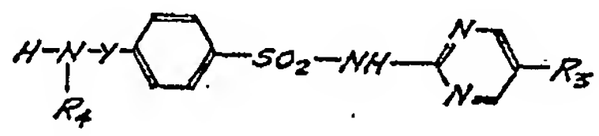


in which R_3 has the meaning given in claim 1 and L represents a halogen atom, a trialkylammonium group or an alkylsulphonyl group containing 1 to 4 carbon atoms, or

d) a compound of the general formula



in which R_1, R_2, n and X have the meanings given in claim 1, or another derivative of the corresponding acid having equivalent reactivity, is reacted with an amine of the general formula



in which R_3, R_4 and Y have the meanings given in claim 1, and, if desired, the resulting compound is converted into a salt thereof with a physiologically tolerable base.

14. A process as claimed in claim 13, wherein Q represents a chlorine atom.

15. A process as claimed in claim 13, wherein L represents a chlorine atom.

16. A process as claimed in claim 13, conducted substantially as described in Example 1 herein.

17. A process as claimed in claim 13, conducted substantially as described in Example 2 or 3 herein.

18. A pharmaceutical preparation which comprises a sulphonamide as claimed in claim 1, in admixture or conjunction with a pharmaceutically suitable carrier.

19. A pharmaceutical preparation which comprises a salt as claimed in claim 2, in admixture or conjunction with a pharmaceutically suitable carrier.

20. A pharmaceutical preparation which comprises the sulphonamide claimed in any one of claims 3 to 9, in admixture or conjunction with a pharmaceutically suitable carrier.

21. A pharmaceutical preparation which comprises the sulphonamide claimed in claim 10 or 11, in admixture or conjunction with a pharmaceutically suitable carrier.

22. A pharmaceutical preparation which comprises a salt as claimed in claim 12, in admixture or conjunction with a pharmaceutically suitable carrier.

ABEL & IMRAY,
Chartered Patent Agents,
Northumberland House,
303—306, High Holborn,
London W.C.1.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1972.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.